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Levetiracetam in children with refractory epilepsy: Lack of correlation between plasma concentration and efficacy

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ABSTRACT

Purpose: The goals of this study are to evaluate the efficacy and tolerability of levetiracetam (LEV) as add-on therapy in children with refractory epilepsies and to determine the value of LEV blood level monitoring in this population.
Methods: Sixty-nine children (39 males and 30 females) treated with LEV between 2006 and 2007 were selected. Their medical files were reviewed for LEV efficacy and tolerability. In a subgroup of children currently taking LEV, plasma concentrations were determined by high performance liquid chromatography by ultraviolet detection (HPLC-UV) method and correlated with the given dose per kilo as well as clinical response.
Results: Fifty-one patients (74%) had a more than 50% reduction in seizure frequency with 16 patients (23%) becoming seizure free on LEV. Eighteen (26%) patients had a less than 50% reduction in seizure frequency. Adverse events due to LEV ranged from mild to moderate in only 18 patients (26%). The most frequently observed were drowsiness, behavioral difficulties, increase in seizure frequency and headaches. The majority (60.5%) of the responders received doses between 10 and 50 mg/kg/day and had a plasma concentration (PC) between 5 and 40 μg/ml. However, we found no clear correlation between PC and efficacy.
Conclusion: Levetiracetam given twice a day in children with refractory epilepsy reduces seizure frequency in all types of epilepsy. In children, LEV is a broad spectrum anticonvulsant with a favourable safety profile.

1. Introduction

Levetiracetam ([S]-α-ethyl-2-oxo-1-pyrrolidine acétamide, LEV, Keppra®, UCB, Belgium), the latest antiepileptic drugs (AED) available in Canada (March 2003), is approved as an add-on therapy to treat refractory partial seizures in children over 4 years old.

It is an enantiopure molecule, the R isomer being inactive. Its structure, which includes a pyrrolidone, resembles that of piracetam. LEV demonstrates pharmacokinetic and clinical profile characteristics desired from an AED: (1) high bio-availability, (2) rapid achievement of steady-state concentrations, (3) linear and time-independent kinetics, (4) limited binding to proteins, (5) minimal metabolism, and (6) benign dose-dependent side effect profile.[1] The specific mechanism of action of LEV has not yet been clearly described, though it has been recognized to be different from traditional AEDs. Recent studies showed that synaptic vesicular proteins (SV2A) have a binding site for LEV.[2,3] Pisani et al. demonstrated with electrophysiological recordings that LEV reduces the amplitude and duration of paroxysmal depolarization shifts during an epileptiform event, as well as the concomitant elevation in $[Ca^{2+}]_i$. Also, patch-clamp recordings revealed that LEV reduces N-, and partially P/Q-type high-voltage-activated Ca^{2+} currents, but not sodium currents.[4] However, other published studies demonstrate that LEV has no affinity for benzodiazepine-associated receptors, nor for gamma-aminobutyric acid (GABA) receptors, re-uptake sites, or second messenger systems.[5,6]

The use of LEV in the pediatric population with pharmacoresistant epilepsy is well documented, yet LEV is not approved in Canada for generalized seizures.[7–14]

The goal of the present study is to better define LEV's therapeutic spectrum, adverse event profile, and optimal therapeutic dosage

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in childhood epilepsies. We retrospectively assessed its therapeutic efficacy in a population of 69 children with epilepsy looking at both seizure reduction and side effects in all types of childhood epilepsies. Then, in a subgroup of children still on LEV, we prospectively looked at the correlation between its plasmatic concentration (PC) and efficacy.

2. Material and methods

2.1. Clinical study

Between July 2006 and June 2007, all patients aged 0–18 years old identified in our database who were treated with LEV at CHU Sainte-Justine's epilepsy clinic, were included in the study. Their medical charts were reviewed and the following clinical data collected: epilepsy syndrome and seizure types, seizure frequency before and after LEV treatment, AEDs currently and previously taken, adverse events, and electroencephalographic (EEG) as well as radiological findings.

2.2. Pharmacokinetic section

Some patients were still taking LEV when recruited. These children and their parents were asked to sign an informed consent form to perform pharmacokinetic studies. A 2–3 ml blood sample in EDTA tubes was taken from the patients. The time to last LEV intake was noted for each individual. The plasma samples were then centrifuged and preserved at −80 °C to be analyzed in our laboratory using high performance liquid chromatography by ultraviolet detection (HPLC-UV).

2.3. Instrumentation

This method has already been described by Martens-Lobenhoffer and Bode-Böger.[15] Briefly, the HPLC system consists of an Agilent 1050 (Agilent Technology company), which includes an automatic sampler, a degasser, a quaternary pomp, a thermostatted column compartment and a variable wavelength detector. The chromatographic separation of the analyte is done on a Thermo Hypercarb (Thermo Electron Company) 150 mm × 4.6 mm (5 μm particle size) analytical column protected with a pre-filter. Data was collected and analyzed using an Agilent ChemStation software package, version 9.01. A LEV stock solution was prepared by dissolving 10 mg of LEV (200 mg provided by UCB: Brussels, Belgium) in 50 ml water. By spiking drug free human plasma with working solution, calibration samples between 100 and 0.781 μg/ml were obtained. This calibration range covered the therapeutic concentration of LEV in our patient samples. A linear regression was done from chromatographic data and allowed us to extrapolate LEV concentration in each patient sample. Quality control samples were prepared in three concentrations levels with target values of 0.781, 6.25 and 50 μg/ml, a mixture of LEV stock solution and drug free human plasma.

From a sample (patient, calibration, blank or quality control), 200 μl were mixed with 20 μl of 1.65 M $HClO_4$ (Fisher Scientific, ON, Canada), 10 μl of 70% $HClO_4$ (both for maximal protein precipitation) and 200 μl of cyclohexane (Fisher Scientific, ON, Canada) (to extract interferences). The samples were vortexed 10 s between each addition. When the mixture was completed, the precipitated proteins were separated by centrifugation at 15 850 × *g* for 30 s. Cyclohexane was aspirated and from the clear aqueous phase, about 100 μl was transferred into autosampler vials containing microliter inserts (C4010-630P, National Scientific Company, TN, USA) and forwarded to the HPLC system.

After injection of 50 μl of the prepared sample into the HPLC system, the separation of LEV was accomplished by gradient elution. Solvent A consisted of 0.423% H_3PO_4 (5 ml H_3PO_4 85% in 1 L water) (Fisher Scientific, ON, Canada), and solvent B of acetonitrile (Fisher Scientific, ON, Canada). The gradient ratio of solvent B started at 5%, raised in 5 min to 30% and finally to 100% for 6 min in order to elute strongly retained substances on the column. After each run, a re-equilibration phase of 4 min was necessary to obtain the starting gradient elution. The flow rate was 1 ml/min and the column temperature was 35 °C. The wavelength detection was set to 205 nm. The retention time of LEV was 4.45 ± 0.10 min under the described conditions.

2.4. Statistical analysis

Data processing and analysis were performed with SPSS Version 14.0 and Graph Pad Prism 4 Version 4.03. All statistical comparisons used exact Fisher tests, χ^2 analysis or Student's *t*-tests for independent samples. Mean values were expressed with their standard error (±S.E.M.). Simple linear regressions were done to correlate LEV plasmatic concentration with dose, time from last dose, weight, gender and age. A one-way ANOVA was done to compare the mean LEV plasmatic concentration in each efficacy group. Curves were compared to evaluate the equivalence of the slopes. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Study population

As shown in Table 1, our group included 69 patients treated with add-on LEV, at a mean age of 12 ± 0.5 years (39 males, 30 females). This included 21 patients (30%) with generalized and 48 (70%) with partial epilepsy. At last follow-up, 11 patients were on LEV monotherapy, 26 were on two AEDs, 21 on 3, 7 on 4, and 4 on 5. Fifty-seven patients (81.4%) were mentally retarded or developmentally delayed.

3.2. LEV efficacy

In our cohort, 51 patients (74%) responded to LEV with a reduction of 50% in seizure frequency (Fig. 1). Sixteen patients (23%) became seizure free. Only 25% of children did not experience a 50% decrease in seizure frequency. Patients with generalized epilepsy had a slightly better outcome than patients with partial epilepsy (86% and 68%, respectively) but this did not reach statistical significance ($p = 0.117$).

Other parameters such as: gender, weight, age, age at diagnosis, seizure type, presence of encephalopathy, presence of co-morbidity, complications during pregnancy, mental retardation or developmental delay, family history of epilepsy, number of AEDs

Table 1
Cohort characteristics at time of the study.

Population	Total population	Drug levels
Number of patients	69	37
Mean age (year)	12 ± 0.5	11.45 ± 0.8
Age range (year)	2.75–20	2.75–18
Male	39	20
Female	30	17
Mental retardation and/or developmental delay	57	30
Number of patients currently on LEV	57	37
LEV PC range (μg/ml)		1.89–74.44
Mean LEV PC (μg/ml)		27.44 ± 3.0
Mean LEV dose (mg/kg/day)		36.30 ± 3.4
Epilepsy type		
Generalized	21	15
Partial	48	22

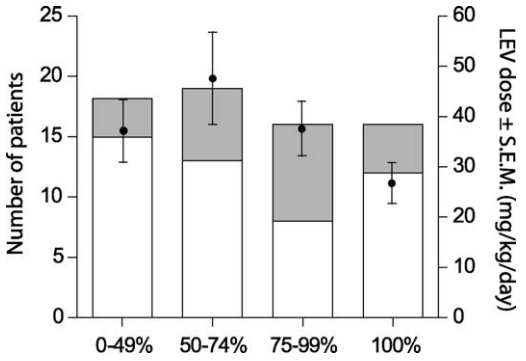

Fig. 1. Impact of LEV on seizure decrease according to epilepsy type. Value ± S.E.M. corresponding to the right *y*-axis represent the mean daily LEV dose. Four categories of efficacy (% of seizure decrease) are represented along the *x*-axis. White bars represent children with partial epilepsy: 15 patients had a reduction in seizure frequency of less than 50% and 33 patients had more than 50% reduction in seizure frequency—including 12 seizure-free (100%). Grey parts represent those with generalized epilepsy: 3 patients had a reduction in seizure frequency of less than 50% and 18 patients had more than 50%—including 4 seizure-free.

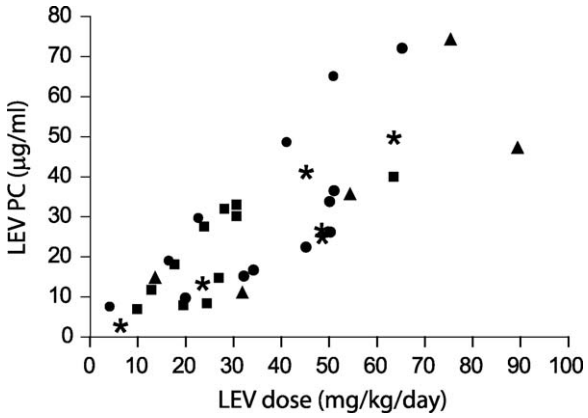

Fig. 3. LEV plasma concentration (PC) in patients suffering from both partial and generalized epilepsy in each efficacy group (symbols), as a function of the daily dose. Stars represent patients with a reduction of seizure frequency ranging from 25 to 49%, triangles from 50 to 74%, circles from 75 to 99%, and squares represent seizure free patients. Data not shown for the only patient with a seizure reduction under 25%.

adjuvant to LEV, number of AEDs taken before LEV and LEV dosage had no significant impact on LEV efficacy.

3.3. Safety

Most children tolerated LEV well. Fifty-one children (74%) reported no adverse event. The most frequently observed adverse events in our population were drowsiness ($n = 8$), behavioral trouble ($n = 5$) characterized by irritability or aggressiveness (all in children with a prior history of behavioral problems), increase in seizure frequency ($n = 3$) and headaches ($n = 2$). Others developed tremor, constipation, increase in body weight, or dizziness (one child in each category) (Fig. 2). Most of these adverse events occurred within a month of treatment onset. Most of the patients required only a reduction in dose to limit these side effects. Overall, only 7 patients had to stop treatment because of the severity of these adverse events. For those who did not stop, the adverse events were determined to be tolerable or resolved over time with continued intake or a dose reduction. An additional 5 children stopped treatment because of a lack of efficacy.

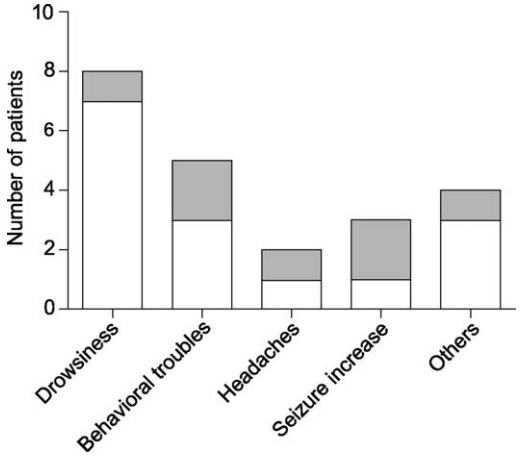

Fig. 2. LEV-induced adverse events. Total bars: patients who suffered from the considered side effect (*x*-axis). Grey parts: patients who stopped the treatment because of the event severity. Total sample includes 69 epileptic children. Some patients known more than one adverse event.

3.4. Pharmacokinetic data

In order to perform therapeutic drug monitoring, blood samples were obtained from 37 children. As shown in Table 1, in this subgroup, the mean age was 11.4 ± 0.8 years, ranging from 2.75 to 18 years old (20 males, 17 females). Sixty percent of patients in this group suffered from partial epilepsy, and 40% from generalized epilepsy. Thirty of the 37 patients evaluated (81%) showed a reduction of seizure frequency of at least 50%, and 11 (30%) were seizure free (Fig. 3). Adverse events occurred in 7 of the 37 patients (19%). The mean LEV plasmatic concentration was 27.44 ± 3.0 µg/ml.

3.5. LEV assimilation and metabolism

We looked at the LEV plasmatic concentration (PC) of the 37 patients, according to dose and time of last intake. The PC correlated linearly ($r^2 = 0.65$, $p < 0.0001$) with the dose, decreased over time in a poorly correlated manner ($r^2 = 0.25$, $p = 0.0043$), and reached non-detectable blood levels around 12 h after intake.

Fig. 3 demonstrates (1) that there is no apparent link between the PC/dose correlation and the epilepsy type (partial: $r^2 = 0.70$; generalized: $r^2 = 0.58$). The PC range in the partial epilepsy group ($n = 22$) was 1.89–74.44 µg/ml and 8.48–72.00 µg/ml in the generalized epilepsy group ($n = 15$).

3.6. LEV efficacy related to dose and PC

The majority (60.5%) of the responders received a LEV dose between 10 and 50 mg/kg/day and had a PC between 5 and 40 µg/ml (Fig. 3). However within this wide range, there was no correlation between PC and efficacy ($p = 0.6$). The PC range of the 11 patients who became seizure free was 6.85–40 µg/ml. While the PC range of the 6 patients who did not respond was 1.89–46.66 µg/ml (Fig. 3).

4. Discussion

The main finding of our study is the high efficacy of LEV in a group of children with refractory epilepsies with limited adverse event. We also confirmed the lack of correlation between efficacy and PC, which could be accounted by the specific mechanism of action on SV2A.

4.1. LEV efficacy

4.1.1. Responder rate

Our response rate is in the higher end of the reported ones in pediatric populations (20–60%).[9,16–18] The proportion of seizure-free patients (23%) is also generally higher than the rates reported by previous studies in children (average of 16%).[10,18–20] This could be due to the retrospective nature of our study, although we included all children from our database who received LEV during the inclusion period. Another possible explanation could be our frequent use of LEV in generalized epilepsies. Although the response rate did not differ significantly between patients with partial or generalized epilepsies, it was higher in the generalized epilepsy group (68% versus 86%, respectively). Children with generalized epilepsy have shown a better response to LEV than children with partial epilepsy in a number of studies.[13,18,21] However, some studies reported that LEV was more effective in the treatment of partial rather than generalized epilepsies, supporting its large spectrum of efficacy.[7,8]

Our high responder rate could also be due to a relatively short follow-up period. However, no data is available to support the development of LEV tolerance in humans, although such an effect has been described in kindled rats.[22]

4.2. LEV predictors of efficacy

Only about a quarter of the patients were considered to be non-responders and 17% discontinued treatment. We therefore could not identify predictors of efficacy in a limited cohort of patients ($n = 69$). The number of patients who failed or stopped treatment due to adverse events or a lack of LEV efficacy is very variable in the literature (9–73% and 6–27%, respectively).[18,19,23] Our study showed that LEV is highly effective in children with generalized epileptic syndromes. Efficacy has also been reported in children with catrastophic epilepsies such as Lennox–Gastaut syndrome and cryptogenic infantile spasms.[24,25]

We studied the influence of clinical parameters on LEV efficacy such as: age, gender, or previous AEDs. In our cohort, no variable was positively correlated with LEV efficacy. Von Stuelpnagel et al. reported that age correlated with LEV response, with patients older than 18 years old responding better than younger patients. This effect of age was not observed within our pediatric population.[18]

Although the vast majority of our refractory patients were developmentally delayed (81%), this did not have a negative impact on the efficacy rate compared to other studies. Moreover, statistical analysis did not reveal any significant relationship between developmental delay and LEV efficacy ($p = 0.175$). This high efficacy of LEV in a mentally handicapped population had also been reported previously.[26]

4.3. Safety

Our study revealed that LEV is an AED with a high tolerability in children, both for partial and generalized epilepsy. Adverse events were observed in 19 patients (27%). The previously reported rates vary from 9.5 to 40%.[14,16–18,19,23] In our population, side effects caused by LEV were mild to moderate, and often reversible (63%) (Fig. 2). Drowsiness was the most commonly reported adverse event and was typically transient. We did not observe gastro-intestinal disorders as other studies reported.[14,20,27,28] The number of patients who stopped treatment due to those side effects was similar to previous studies.[10,20]

As opposed to recent works,[13,29] we found a very low number of patients who experienced an increase in seizure frequency following treatment onset ($n = 3$; 4%). Out of these patients, two had to cease treatment and a dose adjustment allowed the third to continue with LEV therapy. This LEV-induced increase in seizure frequency was observed only in children suffering from partial epilepsy. Whether this represents a natural fluctuation in their seizure pattern or a change due to LEV's mechanism of action is unknown.

4.4. Therapeutic monitoring of LEV

This is the first study to report on therapeutic monitoring of LEV in a pediatric population. Previous studies in adults did not always evaluate the correlation between the LEV PC with the clinical response.[30–32] Our data demonstrates that there is no linear correlation between LEV PC and efficacy. However, we found that 60% of the responders had a LEV PC situated between 5 and 40 μg/ml with no child responding at lower levels, with a daily dose ranging from 10 to 50 mg/kg. These numbers might be used in subsequent studies as a potential therapeutic range for children. The mean LEV PC in our patients is higher than those reported in adults.[33] Other studies also showed a LEV PC range with maximum concentrations that were lower than in ours (e.g. 33.5, 48.2 μg/ml in comparison to 74.44).[31,33] This may be caused by differences in metabolic rates in patients of different age or ethnic background of each population, and to a better tolerability in children. We found no significant correlation between LEV PC and age, gender and epilepsy type in children. These observations suggest these parameters do not affect LEV assimilation, even if there is variability between patients.

5. Conclusion

Our results suggest that LEV is a broad spectrum anticonvulsant in children and can be used with great success also in patients with generalized epileptic syndromes. Its great safety profile, its lack of drug interaction and its efficacy in special populations are novel arguments for its utilization in children with benign as well as refractory epilepsies.

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